

Appl. No. 09/299,562
Amdt. Dated September 8, 2003
Reply to Office Action of April 8, 2003

In the Claims:

This listing of claims will replace all prior application.

Claims 1-23 (canceled)

Claim 24 (withdrawn) *Cancelled* Process for the preparation of a water-pharmaceutical formulation in solid or liquid form according to claims 1 to 23 or a new product according to claims 30 to 37 and of organic solvent-free true aqueous solutions characterized by preparation of true aqueous solutions by way of

- a) dissolving the therapeutically-active compound having low aqueous solubility ($<1.10 \cdot 10^{-4}$ M/Lit, $<1.10 \cdot 10^{-5}$ M/Lit, $<1.10 \cdot 10^{-6}$ M/Lit) and a substantial binding affinity to plasma proteins ("active substance") in a water-miscible, pharmaceutically acceptable organic solvent,
- b) combining said solution with the aqueous solution of the plasma protein fraction in controlled aggregation state
- c) and optionally with a further pharmaceutically acceptable water-soluble auxiliary additive - such as a protein aggregation controller and/or a stabilizer - whereby a true solution is obtained containing the said active substance and the said protein fraction bound together by way of non-covalent bonds;
- d) removing the organic solvent and optionally the water preferably by ultrafiltering, dialysing, diafiltrating and/or lyophilising the solution or its concentrate or by combination of these treatments whereby a homogeneous, water-soluble liquid or solid pharmaceutical product is obtained containing the active substance interlinked with the plasma protein fraction;
- e) optionally dissolving the solid product in water or diluting the liquid product with water whereby a clear, true aqueous solution, free of any organic solvent is obtained which is suitable for therapeutical administration and
- f) optionally finishing this product into a parenteral formulation (dosage form) for direct use.

Claim 25 (withdrawn) Process for the preparation of a water-soluble product or pharmaceutical formulation in solid or liquid form according to any of claims 1 to 23 or a new product according to claims 30 to 37 and their organic solvent-free true aqueous solutions characterized by

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- a) dissolving the active substance in a pharmaceutically acceptable solvent;
- b) combining said solution with a plasma protein fraction in controlled conditions;
- c) said solution containing optionally a pharmaceutically acceptable auxiliary additive - such as a preservative, a stabilizer and/or a stabilizer - whereby a true solution is obtained containing the active substance and the said protein fraction bound together by way of non-covalent interactions;
- d) removing the organic solvent and lyophilising the solution and concentrate.

Claim 26 (withdrawn) A process according to step a) of any of claims 23 to 25 characterized by using to dissolve the active substance a solvent having the following properties:

- a) it is capable to completely dissolve the active substance in its mixture with water and
- b) its mixture with <50% of water does not denaturalize the protein employed.

Claim 27 (withdrawn) A process according to claim 26 characterized by using as the solvent any of the group consisting of an aliphatic C(2-4) monoalcohol or polyalcohol, 70 - 100% ethanol, dimethyl formamide, methyl formamide.

Claim 28 (withdrawn) A process according to step a) of claim 23 to 27 characterized by using as protein aggregation controller or stabilizer and/or solution stabilizing auxiliary additive any of the following agents: water, sodium chloride, a buffer, a poly- alcohol such as glycerol and/or a water-soluble sugar derivative preferably mannitol, sorbitol and/or dulcitol.

Claim 29 (withdrawn) A process according to step a) of any of claims 23 to 28 characterized by using paclitaxel and a component of the natural plasma such as serum albumin, an immunoglobulin, glycoprotein, interferon and/or interleukin or a recombinant of the same.

Claims 30-90 (canceled)

Claim 91 (withdrawn) A method of treating a human or veterinary patient in need thereof with the pharmaceutical composition of claim 1, comprising the

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step of administering an effective amount of said pharmaceutical composition to the patient.

Claim 92 (withdrawn) The method of treatment according to claim 91 wherein the following effective amounts are administered (calculated on the therapeutically-active compound): paclitaxel and albumin 70-280 mg per treatment; propofol and albumin 6-10 mg per kG per hour; camptothecin and albumin, gemfibrozil and albumin, cyclosporin A and albumin 3-5 mg per kG per day; amphotericin B and albumin up to 1.5 mg per kG per day.

Claims 93-95 (canceled)

Claims 96-140 ~~(not entered)~~ cancelled

Claim ~~141~~ 1 (New) A pharmaceutical composition for parenteral use, comprising:

- a) a therapeutically-active compound having
 - i) an aqueous solubility of less than about 1×10^{-4} molar; and
 - ii) a substantial binding affinity to plasma proteins wherein greater than about 90% of the therapeutically-active compound is protein bound in spontaneous equilibrium at room temperature; and
- b) a plasma protein in controlled aggregation state selected from the group consisting of serum albumin and gamma globulin, wherein greater than about 98% of the therapeutically-active compound is non-covalently bound to the plasma protein in a water-soluble product.

Claim ~~142~~ 2 (New) The pharmaceutical composition of claim ~~141~~ 1, wherein the pharmaceutical composition is a water-soluble solid product.

Claim ~~143~~ 3 (New) The pharmaceutical composition of claim ~~141~~ 1, wherein the pharmaceutical composition is a lyophilized product.

Claim ~~144~~ 4 (New) The pharmaceutical composition of claim ~~141~~ 1, wherein the pharmaceutical composition is an aqueous solution.

Claim ~~145~~ 5 (New) The pharmaceutical composition of claim ~~141~~ 1, wherein the plasma protein is a human plasma protein.

Claim ~~146~~⁶ (New) The pharmaceutical composition of claim ~~141~~¹, wherein the plasma protein is an animal plasma protein.

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Claim ~~147~~⁷ (New) The pharmaceutical composition of ~~141~~¹, wherein the plasma protein is a recombinant plasma protein.

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Claim ~~148~~⁸ (New) The pharmaceutical composition of ~~141~~¹, wherein the therapeutically-active compound is present in a mole/mole ratio to the plasma protein within the range of 1:0.05 to 1:100.

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Claim ~~149~~⁹ (New) The pharmaceutical composition of ~~141~~¹, wherein the therapeutically-active compound is present in a mole/mole ratio to the plasma protein within the range of 1:0.1 to 1:50.

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Claim ~~150~~¹⁰ (New) The pharmaceutical composition of ~~141~~¹, wherein the therapeutically-active compound is PACLITAXEL[®] and the plasma protein is human serum albumin.

Claim ~~151~~¹¹ (New) The pharmaceutical composition of claim ~~150~~¹⁰, wherein the therapeutically-active compound is 1 mg/ml PACLITAXEL[®] in absolute ethanol and the plasma protein is 20% aqueous solution of human serum albumin.

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Claim ~~152~~¹² (New) The pharmaceutical composition of ~~150~~¹⁰, wherein the therapeutically-active compound is 2 mg/ml PACLITAXEL[®] in absolute ethanol and the plasma protein is 4.44% aqueous solution of human serum albumin.

Claim ~~153~~¹³ (New) The pharmaceutical composition of claim ~~141~~¹, wherein the therapeutically-active compound is PACLITAXEL[®] and the plasma protein is recombinant human serum albumin.

Claim ~~154~~¹⁴ (New) The pharmaceutical composition of claim ~~153~~¹³, wherein the therapeutically-active compound is 2.0 mg/ml PACLITAXEL[®] in absolute ethanol and the plasma protein is 4.44% aqueous solution of recombinant human serum albumin.

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Claim ~~155~~ ¹⁵ (New) The pharmaceutical composition of ~~141~~ ^{claim 1}, wherein the therapeutically-active drug solution is PACLITAXEL® and the plasma protein is human gamma globulin.
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Claim ~~156~~ ¹⁶ (New) The pharmaceutical composition of ~~155~~ ^{claim 15}, wherein the therapeutically-active drug solution is 0.1 mg/ml PACLITAXEL® in absolute ethanol and the plasma protein is 2.25% aqueous solution of human gamma globulin.
- Claim ~~157~~ ¹⁷ (New) The pharmaceutical composition of claim ~~141~~ ¹, wherein the therapeutically-active compound is AMPHOTERICIN B® and the plasma protein is human serum albumin.
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Claim ~~158~~ ¹⁸ (New) The pharmaceutical composition of ~~157~~ ^{claim 17}, wherein the therapeutically-active compound is 4.0 mg/ml AMPHOTERICIN B® in dimethyl formamide and the plasma protein is 0.8% aqueous solution of human serum albumin.
- Claim ~~159~~ ¹⁹ (New) The pharmaceutical composition of claim ~~141~~ ¹, wherein the therapeutically-active compound is AMPHOTERICIN B® and the plasma protein is recombinant human serum albumin.
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Claim ~~160~~ ²⁰ (New) The pharmaceutical composition of ~~159~~ ^{claim 19}, wherein the therapeutically-active compound is 40.0 mg/ml AMPHOTERICIN B® in dimethyl formamide and hydrochloric acid and the plasma protein is 0.8% aqueous solution of recombinant human serum albumin.
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Claim ~~161~~ ²¹ (New) The pharmaceutical composition of ~~141~~ ^{claim 1}, wherein the therapeutically-active compound is camptothecin and the plasma protein is human serum albumin.
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Claim ~~162~~ ²² (New) The pharmaceutical composition of ~~161~~ ^{claim 21}, wherein the therapeutically-active compound is 0.14 mg/ml camptothecin in absolute ethanol and the plasma protein is 0.4% aqueous solution of human serum albumin.
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Claim ~~163~~ ²³ (New) The pharmaceutical composition of ~~141~~ ^{claim 1}, wherein the therapeutically-active compound is camptothecin and the plasma protein is recombinant human serum albumin.

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Claim ~~164~~ ²⁴ (New) The pharmaceutical composition of ~~163~~ ^{claim 23}, wherein the therapeutically-active compound is 0.14 mg/ml camptothecin in absolute ethanol and the plasma protein is 0.4% aqueous solution of recombinant human serum albumin.
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Claim ~~165~~ ²⁵ (New) The pharmaceutical composition of ~~141~~ ^{claim 1}, wherein the therapeutically-active compound is CARBAMAZEPIN® and the plasma protein is human serum albumin.
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Claim ~~166~~ ²⁶ (New) The pharmaceutical composition of ~~165~~ ^{claim 25}, wherein the therapeutically-active compound is 8.0 mg/ml CARBAMAZEPIN® in absolute ethanol and the plasma protein is 4.0% aqueous solution of human serum albumin.
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Claim ~~167~~ ²⁷ (New) The pharmaceutical composition of ~~141~~ ^{claim 1}, wherein the therapeutically-active compound is cyclosporine A and the plasma protein is human serum albumin.
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Claim ~~168~~ ²⁸ (New) The pharmaceutical composition of ~~167~~ ^{claim 27}, wherein the therapeutically-active compound is 1.0 mg/ml cyclosporine A in absolute ethanol and the plasma protein is 4.0% aqueous solution of human serum albumin.
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Claim ~~169~~ ²⁹ (New) The pharmaceutical composition of ~~141~~ ^{claim 1}, wherein the therapeutically-active compound is cyclosporine A and the plasma protein is recombinant human serum albumin.
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Claim ~~170~~ ³⁰ (New) The pharmaceutical composition of ~~169~~ ^{claim 29}, wherein the therapeutically-active compound is 1.0 mg/ml cyclosporine A in absolute ethanol and the plasma protein is 2.0% aqueous solution of recombinant human serum albumin.
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Claim ~~171~~ ³¹ (New) The pharmaceutical composition of ~~141~~ ^{claim 1}, wherein the therapeutically-active compound is cyclosporine A and the plasma protein is human gamma globulin.
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Claim ~~172~~ ³² (New) The pharmaceutical composition of ~~171~~ ^{claim 31}, wherein the therapeutically-active compound is 1.0 mg/ml cyclosporine A in absolute ethanol and the plasma protein is 2.25% aqueous solution of human gamma globulin.

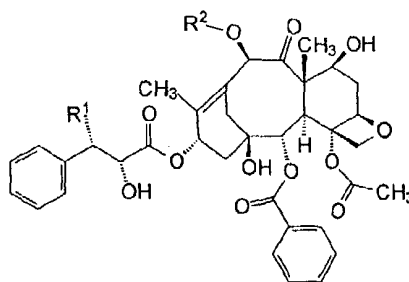
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Claim 173³³ (New) The pharmaceutical composition of ~~141~~^{Claim 1}, wherein the therapeutically-active compound is PROPOFOL[®] and the plasma protein is human serum

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Claim 174³⁴ (New) The pharmaceutical composition of ~~173~~^{Claim 33}, wherein the therapeutically-active compound is 2.0 mg/ml PROPOFOL[®] in absolute ethanol and the plasma protein is 0.4% aqueous solution of human serum albumin.

Claim 175³⁵ (New) The pharmaceutical composition of 141, wherein the therapeutically-active compound is PROPOFOL[®] and the plasma protein is recombinant

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Claim 176³⁶ (New) The pharmaceutical composition of ~~175~~^{Claim 35}, wherein the therapeutically-active compound is 2.0 mg/ml PROPOFOL[®] in absolute ethanol and the plasma protein is 0.4% aqueous solution of recombinant human serum albumin.

Claim 177³⁷ (New) The pharmaceutical composition of claim ~~141~~¹, wherein the therapeutically-active compound is a taxonoid of the general formula I



wherein R₁ represents tert. butyl-oxy-carboxylic acid amide or benzoyl amide, and R₂ represents hydrogen or an acyl group.

Claim 178³⁸ (New) The pharmaceutical formulation of claim ~~177~~³⁷, wherein the acyl group is an acetyl group.

Claim 179³⁹ (New) The pharmaceutical composition of claim ~~141~~¹, wherein the pharmaceutical formulation is an organic solvent-free aqueous solution.

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Claim ~~180~~⁴⁰ (New) The pharmaceutical composition of claim ~~141~~¹, wherein the pharmaceutical composition is an injectable form suitable for parenteral administration.

Claim ~~181~~⁴¹ (New) The pharmaceutical composition of claim ~~141~~¹, prepared by the process comprising the steps of:

- a) dissolving a therapeutically-active compound in a water-miscible, pharmaceutically acceptable organic solvent;
- b) dissolving a plasma protein in an aqueous solution;
- c) adding the organic solvent in step a) to the aqueous solution in step b);
- d) removing the organic solvent.